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10/574,961	07/05/2006	Stefan Knackmuss	6713/PCT	9714

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BREINER & BREINER, L.L.C.
P.O. BOX 320160
ALEXANDRIA, VA 22320-0160

EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,961	KNACKMUSS ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *3-8,11,14-23 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2, 9,10,12,13 and 24-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/16/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received November 29, 2007.

Election/Restrictions

Applicant's election without traverse of group I, claims 1, 2, 9, 10, 12, 13, 24-36 is acknowledged. Upon further consideration the restriction requirement between groups I and II is withdrawn. The single chain antibody molecules of SEQ ID NO: 2 and SEQ ID NO: 4 are subject to **species election**. SEQ ID NO: 4, which is claims 5 and 6 will be examined once the generic claim is found allowable.

Claims 3, 4, 5, 6, 7, 8, 11, 14-23, and 37 are withdrawn because the claims are drawn to the non-elected invention. Claims 1, 2, 9, 10, 12, 13, and 24-36 are under examination in the present Office action as they read on elected invention.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on October 8, 2003. It is noted, however, that applicant has not filed a certified copy of the Germany 103 46 627 application as required by 35 U.S.C. 119(b). Applicant should provide an original certified copy of the Germany 103 46 627 document or to provide a proof that the document was provided to WIPO at the international stage.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 16, 2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner. The Gesundheitsforschung document has not been considered because the English translation has not been provided.

Claim Objections

Claim 1 is objected to because of the following informalities: The claims use abbreviations LRP/LR. The Laminin Receptor Precursor/ Laminin Receptor should be spelled out before the first use of the abbreviation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 9, 10, 12, 13, and 24-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to single chain antibody molecules of SEQ ID NO: 2 and homologs thereof and homologs of the fragments. The antibody molecule is modified by one or more amino acid exchanges, deletions, and insertions increasing the stability or changing the biophysical and/or biochemical properties. The single chain antibody molecules of SEQ ID NO:

2 and SEQ ID NO: 4 are modified to increase the stability and for changing the biophysical and/or biochemical properties by post-translational modifications such as glycosylation, phosphorylation, amidation or acylation.

There is insufficient written description of the genus encompassed by the recitation of **1)** the homologs and homologs of the fragments, and the **2)** antibody molecules comprising deletions, insertions, and post-translational modifications.

The specification defines the claimed homologs as:

> [0024] A homolog of the antibody molecule which comprises the amino acid sequence SEQ ID No. 2 or 4 is customarily homologous to at least 70%, preferably to 80 or 90% and in particular to 95%, to the antibody molecule comprising the amino acid sequence SEQ ID No. 2 or 4 over a region of at least 60, 80 or 100 or more adjacent amino acids.

The present claims require that the recited deletions, insertions, and post-translational modifications would result in changing the biophysical and/or biochemical properties of the single chain antibody molecules. However, the claims do not recite a function of the antibody molecules which biophysical and/or biochemical properties have been changed by deletions, insertions, and post-translational modifications. The specification lacks written description with regard to which amino acids within the single chain antibodies should be maintained/conserved in order for the antibody molecules to bind the laminin receptor. Thus without an adequate written description with regard to which amino acids molecules can be deleted, or substituted for within the 279 amino acid long antibody molecules of SEQ ID NO: 2 and 4, the skilled artisan would be unable to determine the structures of the claimed antibody homologs. There is lack of

an adequate structure and function correlation with regard to the claimed genus of antibody homologs and antibodies comprising amino acid deletions, substitutions and other modifications.

It is known in the art that amino acid deletions or insertions can alter the function of an antibody so that the antibody will no longer bind antigen of interest. For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991; see entire document) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 77: 3211-3214, 1980; see entire document) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Therefore, the specification does not provide for sufficient written description to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of SEQ ID NO: 2 and 4 antibody homologs and antibodies comprising amino acid deletions, insertions or other chemical modifications.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C § 112, paragraph 1 "Written Description" requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January, 2001, See especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) Consequently, Applicant was not in possession of the instant claimed invention. See *University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

The skilled artisan cannot envision the detailed structure of a genus of homologs and homologs of the fragments of single chain antibody molecules that are contemplated in the invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim 1, 2, 9, 10, 12, 13, and 24-36 are rejected under 35 U.S.C. 112, first paragraph, because **1)** the specification, while being enabling for single chain antibody molecules of SEQ ID NO: 2 and SEQ ID NO: 4 and their fragments binding the laminin receptor precursor and laminin receptor (LRP/LR), does not reasonably provide enablement for fragments of SEQ ID NO: 2 and SEQ ID NO: 4 that do not bind the LRP/LR antigens. **2)** The specification, while being enabling for a pharmaceutical composition comprising antibodies of SEQ ID NO: 2 and SEQ ID NO: 4 used for detection of specific antigens in body fluids, does not reasonably provide enablement for a pharmaceutical composition for treatment of prion diseases.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims are drawn to single chain antibody molecules of SEQ ID NO: 2 and SEQ ID NO: 4 and homologs or fragments thereof and homologs of the fragments. Claims are drawn to a pharmaceutical composition comprising single chain antibody molecules suitable for treatment of prion disease.

The claims are rejected because the specification does not provide sufficient enablement for the claimed fragments and homologs of the fragments of SEQ ID NO: 2 and SEQ ID NO: 4. The specification does not provide sufficient enablement for the pharmaceutical compositions suitable for treatment of prion disease.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, that quantity of experimentation necessary, the (un)predictability of the art, and the breadth of the claims.

Claims are broadly drawn to fragments of the single chain antibodies of SEQ ID NO: 2 and SEQ ID NO: 4. The claims do not require that the claimed fragments and homologs of the fragments bind any specific antigen. Therefore the claims broadly read on fragments and homologs of the fragments that might not bind antigen. Claims are broadly drawn to a pharmaceutical composition comprising single chain antibody molecule and suitable for treatment of prion disease. It is noted that neither the full length antibody molecules of SEQ ID NO: 2 and 4, nor their fragments and homologs of the fragments are enabled for treatment of prion disease. With regard to the diagnostic composition comprising antibody molecules of SEQ ID NO: 2 and 4, the diagnostic compositions comprising antibody molecules of SEQ ID NO: 2 and 4 are enabled; however the diagnostic composition comprising fragments and fragment homologs of SEQ ID NO: 2 and 4 are not enabled.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. It is known in the art that even minor changes in the amino acid sequences of the heavy and light variable

regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Single amino acid substitution altering antigen-binding specificity. PNAS, 1982, Vol 79, p. 1979-1983). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Panka et al. (Variable region framework differences result in decreased or increased affinity of variant anti-digoxin antibodies, PNAS, 1988, Vol. 85, p. 3080-3084) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. Thus considering the knowledge in the art and the known fact that even minor amino acid substitutions my alter the affinity of the antibody to bind antigen, the skilled artisan would be required to conduct an undue amount of experimentation in order to determine which amino acid substitutions and/or modifications are permissible and would not affect the binding of the single chain antibodies to the laminin receptor antigen. It is noted that Laminin is a glycoprotein of the extracellular matrix, where it is involved in the adhesion, motion, differentiation and growth of cells. The pathogenic for of prion is known to bind to the laminin receptor.

The present specification provides working examples showing binding of the single chain monoclonal antibody of SEQ ID NO: 2 to the 67 kDa form of the laminin receptor in the leukocyte fraction of the blood and cerebrospinal fluid of cattle suffering from BSE (Example 3, and Figures 14 and 15). Thus the specification shows that the single chain antibody of SEQ ID NO: 2 can recognize an increased level of the 67 kDa form of the laminin receptor. The specification does not provide working examples showing the binding of modified single chain antibody fragments and homologs of the fragments of SEQ ID NO: 2 to the laminin receptor.

The specification contemplates using the singe chain antibodies in methods of treating prion disease comprising administering single chain antibodies to animals in vivo. However the specification does not provide working examples showing administration of single chain antibodies in animals or the effects of such in vivo treatment. Thus in view of the absence of an evidence showing positive effects of in vivo administration of the anti-laminin receptor antibodies in animals, the skilled artisan would be unable to positively conclude that administration of anti-laminin receptor antibodies could have any positive effects in treatment of prion disease. The specification provides no description and exemplification of how to use the pharmaceutical composition, without undue experimentation, for the treatment of prion disease in animal or humans. The working examples provided do not give sufficient guidance to allow one skilled in the art to practice the full scope of the invention with a reasonable expectation of success.

Irani et al. (Annual Reviews in Medicine, 2003, Vol. 54, p. 305-319.) and Coulthart et al. (Canadian Medical Association, 2001, Vol. 165, p.51-58) reviews the research efforts in the field of diagnosis and treatmentof prion diseases. Currently, there is no treatment or preventive means for prion disease. Because of a very long time period (more than 10 years in humans) which elapses between infection and the appearance of the first clinical symptoms, and because the diagnosis can be only performed postmortem, it would have been nearly impossible to evaluate the efficacy of the prevention of the prion diseases in humans (Georgieva, Experimental Pathology and Parasitology, 2002, p. 60-63).

Thus, the nature of the invention and the state of prior art have not provided reasonable expectation of success in the treatment of prion diseases. For the above discussed reasons, it

appears that undue experimentation would be required to practice the claimed invention. In conclusion, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately determine whether the compositions of the instant application do in fact have a therapeutic effect against prion disease. The skilled artisan would be required to conduct an undue amount of experimentation in order to accurately determine which homologs and homologs of the fragments of SEQ ID NO: 2 would maintain the function of the single chain antibody to bind laminin receptor or laminin receptor precursor.

Thus, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments regarding the therapy and prevention of prion diseases, that one of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately extrapolate whether said composition would actually have a therapeutic effect against prion disease.

As discussed above undue experimentation would be required to practice the claimed invention commensurate with the scope of the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Conclusion

SEQ ID NO: 2 is free of prior art of record.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Agnieszka Boesen, Ph.D.

/Stacy B. Chen/ 2-4-2008
Primary Examiner, TC1600